PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Wilhelmus Everhardus Hennink, Cornelus Franciscus van Nostrum, and Silvia Johanna de Jong

Examiner: B. Fubara

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Dated: January 20, 2005

For: Stereocomplex hydrogels

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I hereby certify this correspondence is being deposited with the United States Postal Service as first class mail, postpaid in an envelope, addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450
on January 20, 2005

Signature: _____

DECLARATION UNDER 37 CFR 1.132

I Wilhelmus Everhardus Hennink of Zuidplaslaan 120 NL-2743 CZ Waddinxveen, the Netherlands declare as follows.

1. I am employed by the University of Utrecht as professor. I am an expert in the field of hydrogel compositions, as evidenced by the *curriculum vitae* attached hereto as Exhibit A. I am an inventor in the present application and am also a co-inventor in WO 98/00170

2. I have reviewed the Office Action mailed by the Examiner on October 20, 2004, and the references cited by the Examiner in the Office Action. This declaration is being submitted in response to the Office Action to distinguish the present invention from the prior art references.

3. In accordance with the invention, a hydrogel is formed by mixing aqueous solutions or dispersing of a water-soluble or dispersible polymer (e.g. dextran) to which oligomers of opposite chirality are grafted or otherwise substituted. By this process a physically linked hydrogel is obtained.
Stereocomplex formation between poly(D-lactic acid) and poly(L-lactic acid) has been demonstrated in the prior art to occur when these polymers are dissolved in a suitable organic solvent (e.g. dichloromethane) followed by evaporation of the solvent.
We were the first who demonstrated that stereocomplexes can be formed by mixing aqueous solutions/dispersions of a water-soluble or dispersible polymer (e.g. dextran) to which oligomers of opposite chirality are substituted (preferably grafted).

4. One of the important aspects distinguishing the subject-matter of present claims from the cited references of Okihara et al. (J. Macromol. Sci. Phys (1990) B30 (1 & 2) 119-140) and WO 98/00170 (in the name of the undersigned) is that the present claims relate to a hydrogel composition comprised of a mixture of two types of water soluble or water dispersible polymers that are substituted with oligomers or co-oligomers, wherein the (co-)oligomers in the first polymer are at least partly formed from chiral monomers and wherein the (co-)oligomers in the second polymer are at least partly formed from chiral monomers with a chirality that is opposite to that of said monomers in the first polymer, such that the chiral part of the (co-)oligomers are in essence complementary to that in the first polymer.

5. Okihara et al. does not disclose a hydrogel. Firstly, no water is present in the described system. Hence, it is impossible to have a hydrogel present.

6. Secondly, Okihara et al. does not disclose water soluble polymers. The Examiner states (on page 2 and also other pages) that "polymers of lactic acid and glycolic acid are water-soluble; at the worst they are sparingly soluble". This statement is incorrect. Poly(lactic acid) and its copolymers with glycolic acid are not soluble in water, but they only

dissolve in organic solvents. Confusingly, these polymers are sometimes called water-soluble in literature, but this characteristic refers to the ability of these polymers to degrade to low molecular weight degradation products when solid specimens of these polymers are placed in an aqueous solution. The degradation products may be water-soluble. The polymer itself is not. This degradation process takes from a few weeks to a years, depending on a great number of factors) (see e.g. Hennink WE, Van Steenis, JH and Van Nostrum CF. Fast degradable polymers. In: Reflexive Polymers and Hydrogels. In: Understanding and designing fast responsive polymeric system. Ed: Yui, N. Mrsny RJ, and Park K. CRC Press page 401-423, 2004). This alleged "water-solubility" is something completely different from the physico-chemical definition of solubility (i.e. the generally used definition).

7. Thirdly, Okihara et al. does not disclose polymers substituted with an oligomer. Okihara et al. discloses non-substituted homopolymers.

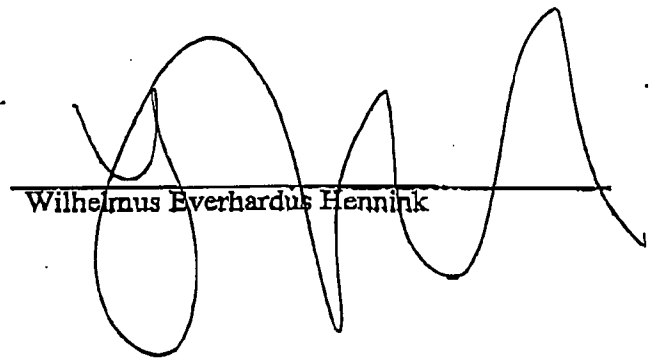
8. WO 98/00170 does not disclose a hydrogel comprising two different substituted polymers, wherein the chiral parts of the substituents are in essence complementary to each other either.

9. The only reference made to the isomeric form of the lactide is in Example 3, which describes the synthesis of dex-lactate-HEMA by coupling L-lactide and HEMA thereby forming HEMA-lactate, and coupoling the HEMA-lactate to dextran. In this example the lactate is used as a hydrolysable spacer and not as a chiral substituent of a water soluble polymer that interacts noncovalently with another polymer having a lactide substituent of opposite chirality. Thus, WO 98/00170 fails to describe a gel using two types of polymers, each having a chiral substituent that is complementary to the other. Furthermore, unlike the invention as claimed, the hydrogels in WO 98/00170 are prepared by free radical polymerization of a crosslinkable group such as methacrylate, acrylate, vinyl ethers and vinyl esters, resulting in the formation of covalent bonds.

10. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true. Further that these statements were made with the knowledge that willfully false statements, and the like, so made are punishable by fine or imprisonment or both under Section 1001 of Title 18

of the United States Code, and that such willfully false statements may jeopardize the validity of the application of any patent issued thereon.

Date: Jan 20th 2005



Wilhelmus Everhardus Hennink